Silent ischemic infarcts are associated with hemorrhage burden in cerebral amyloid angiopathy

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ABSTRACT

Background: Neuropathologic studies suggest an association between cerebral amyloid angiopathy (CAA) and small ischemic infarctions as well as hemorrhages. We examined the prevalence and associated risk factors for infarcts detected by diffusion-weighted imaging (DWI).

Methods: We performed retrospective analysis of MR images from 78 subjects with a diagnosis of probable CAA and a similar aged group of 55 subjects with Alzheimer disease or mild cognitive impairment (AD/MCI) for comparison. DWI and apparent diffusion coefficient (ADC) maps were inspected for acute or subacute infarcts. We also examined the association between DWI lesions and demographic variables, conventional vascular risk factors, and radiographic markers of CAA severity such as number of hemorrhages on gradient-echo MRI and volume of T2-hyperintense white matter lesions.

Results: Twelve of 78 subjects with CAA (15%) had a total of 17 DWI-hyperintense lesions consistent with subacute cerebral infarctions vs 0 of 55 subjects with AD/MCI ($p = 0.001$). The DWI lesions were located primarily in cortex and subcortical white matter. CAA subjects with DWI lesions had a higher median number of total hemorrhages (22 vs 4, $p = 0.025$) and no difference in white matter hyperintensity volume or conventional vascular risk factors compared to subjects with CAA without lesions.

Conclusions: MRI evidence of small subacute infarcts is present in a substantial proportion of living patients with advanced cerebral amyloid angiopathy (CAA). The presence of these lesions is associated with a higher burden of hemorrhages, but not with conventional vascular risk factors. This suggests that advanced CAA predisposes to ischemic infarction as well as intracerebral hemorrhage. ***Neurology*® 2009;72:1230–1235**

GLOSSARY

AD = Alzheimer disease; **ADC** = apparent diffusion coefficient; **CAA** = cerebral amyloid angiopathy; **DWI** = diffusion-weighted imaging; **FLAIR** = fluid-attenuated inversion recovery; **GRE** = gradient-echo; **HTN** = hypertension; **ICH** = intracerebral hemorrhage; **MCI** = mild cognitive impairment; **MGH** = Massachusetts General Hospital; **nWMH** = normalized white matter hyperintensity volumes; **WMH** = white matter T2-hyperintense lesions.

Cerebrovascular deposition of amyloid (cerebral amyloid angiopathy [CAA]) is most commonly recognized as a cause of spontaneous lobar intracerebral hemorrhage (ICH).[1] Neuropathologic studies have also identified ischemic infarctions in association with advanced CAA.[2-7] CAA-associated ischemic infarcts are reported as small, primarily located in the cortex or subcortical white matter, and clinically asymptomatic.[2-4,6,7]

Given the substantial contribution of small, apparently silent infarcts to cognitive impairment,[8,9] identifying CAA-associated ischemic infarction in living patients could be an important step toward unraveling this pathology's effects on cognition. Imaging studies of CAA subjects have previously demonstrated other possible correlates of cerebral ischemia such as white matter T2-hyperintense lesions (WMH)[10,11] and loss of normal cerebrovascular reactivity,[12] but not ischemic infarcts themselves.

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Utilizing the ability of diffusion-weighted imaging (DWI) to detect small acute or subacute infarctions,[13] we undertook a systematic retrospective analysis of DWI images obtained from CAA subjects. We sought to determine whether lesions suggestive of ischemic infarction were more prevalent in subjects with advanced CAA than similar aged control subjects with Alzheimer disease (AD) or mild cognitive impairment (MCI). We also predicted that if advanced CAA was indeed a cause of ischemic infarction, these lesions might be associated with other markers of CAA severity such as number of hemorrhages or WMH volume.

METHODS

Study participants. We performed a retrospective, cross-sectional analysis of lesions on DWI and apparent diffusion coefficient (ADC) MRI sequences among 78 subjects with CAA and a control group of 55 subjects with AD or MCI without evidence of CAA. AD/MCI subjects were selected as a control group because of their similarity in age and vascular risk factors to the CAA subjects and the availability of MRI scans with DWI sequences.

The CAA subjects represented consecutive patients enrolled at Massachusetts General Hospital (MGH) between February 1999 and June 2008 in an ongoing prospective longitudinal cohort study of CAA[14] as well as all patients enrolled at MGH between February 2003 and October 2003 (but not yet randomized to treatment) in a phase 2 double-blinded trial of tramiprosate for CAA.[15] Participants were eligible for the current study if they underwent MR imaging and met Boston criteria for probable or definite CAA.[16] The Boston criteria exclude subjects for hemorrhages in deep hemispheric regions such as basal ganglia or thalamus or for definite secondary cause of hemorrhage such as head trauma, brain tumor, vasculitis, vascular malformation, or excessive anticoagulation. Additional exclusion criteria for the current study were absence of one of the required MRI sequences (gradient-echo [GRE], fluid-attenuated inversion recovery [FLAIR], DWI, or ADC maps), motion-degraded artifacts precluding interpretation of one of the required sequences, acute neurologic symptoms (other than those related to the subject's ICH) suggestive of acute ischemic stroke, or a diagnosis of CAA-related inflammation.[17] Of 96 probable CAA subjects enrolled during this time interval (86 from the longitudinal cohort, 10 from the tramiprosate trial), 18 were excluded (all but one from the longitudinal cohort): 13 for absence of one of the required MRI sequences, 2 for motion-degraded images, 1 for acute neurologic symptoms, and 2 for CAA-related inflammation. Of the remaining 78 CAA subjects analyzed in the current study, 63 (81%) had a history of intracerebral hemorrhage. The remaining 15 subjects initially presented with symptoms other than acute intracerebral hemorrhage (memory impairment, seizure, gait impairment, episodic confusion, or transient sensory symptoms).

AD/MCI subjects were patients seen in the Memory Disorders Unit of MGH who participated in a research study of biomarkers.[18] Subjects received a diagnosis of probable AD by National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria[19] or of MCI (amnestic or multiple domain) by Peterson criteria.[20] Eligibility criteria for inclusion in the current study were MRI scan that included the above sequences and absence on GRE of lobar microbleeds[21] suggestive of accompanying advanced CAA. Of 118 consecutive patients seen in the Memory Unit between 2002 and 2004 and screened for eligibility, 51 were excluded for absence of one of the required sequences and 12 for the presence of lobar microbleeds, yielding 55 control subjects (41 with probable AD, 14 with MCI) for the final study analysis.

Among the final group of 78 CAA subjects, the indications for MRI were acute hemorrhage (<7 day post-ICH) in 38, routine follow-up of a prior hemorrhage (at least 1 month post-ICH) in 18, nonspecific symptoms (dizziness or confusion) in 7, chronic memory loss in 5, and as pretreatment baseline for a drug trial[15] in 10. Among the final group of 55 AD/MCI subjects, the indication for MRI was routine evaluation of memory loss in 49, nonspecific symptoms (dizziness or confusion) in 3, and recent worsening of confusion in 3.

All subjects provided informed consent for participation in the above research studies and all aspects were approved by the hospital Institutional Review Board.

Data collection. Demographic information (age at time of brain MRI and gender) and presence of vascular risk factors (hypertension [HTN], diabetes, coronary artery disease, dyslipidemia, tobacco use) were ascertained by review of the medical records. Cognitive status of the CAA subjects prior to initial presentation was determined as described[22] by structured interview with family members using a standardized questionnaire with items related to memory, praxis, calculation, and reasoning. HTN was defined as use of an antihypertensive medication; we also identified use of more than one antihypertensive medication as a marker of relatively severe HTN. Diabetes was defined as ongoing use of a hypoglycemic agent. Coronary artery disease was defined as history of a myocardial infarction, history of a coronary revascularization, or evidence of coronary artery stenosis based on cardiac stress testing or cardiac catheterization. Ischemic stroke was defined by documented history of stroke symptoms with supportive neuroimaging. Dyslipidemia was defined by documented diagnosis of this disorder in the subject's medical record. Tobacco use included both ongoing and past use. APOE genotype was analyzed as previously described[14] in the 39 subjects with available DNA samples from the 78 CAA subjects.

MRI acquisition and analysis. All subjects underwent MRI examination of the brain on a 1.5 Tesla Signa scanner (GE Medical Systems, Milwaukee, WI) as previously described.[11] Diffusion-weighted images (repetition time/echo time 7,500/99.3 msec, slice thickness 6 mm, interslice gap 1.5 mm, 128 × 128; b value = 1,000 s/mm^2) were acquired in the X, Y, and Z dimensions and averaged to generate absolute diffusion values largely independent of anisotropic diffusion. Diffusion-weighted images were viewed with AMICAS clinical imaging software (Boston, MA), which incorporates a bilinear interpolation to smooth the borders between individual pixels. FLAIR and GRE images were obtained using previously reported parameters.[11,23]

All images were reviewed by an experienced reader (W.T.K.) for the presence and number of hyperintensities on DWI. If more than one MRI containing the required sequences was available for a subject, the most recent scan was used. Lesions were considered DWI-positive if hyperintense on this sequence relative to surrounding tissue and distinct from any recent intracerebral hemorrhage. The corresponding region on the ADC map was also viewed to confirm that the diffusion coefficient was

Table 1 Characteristics of subjects with CAA or AD/MCI

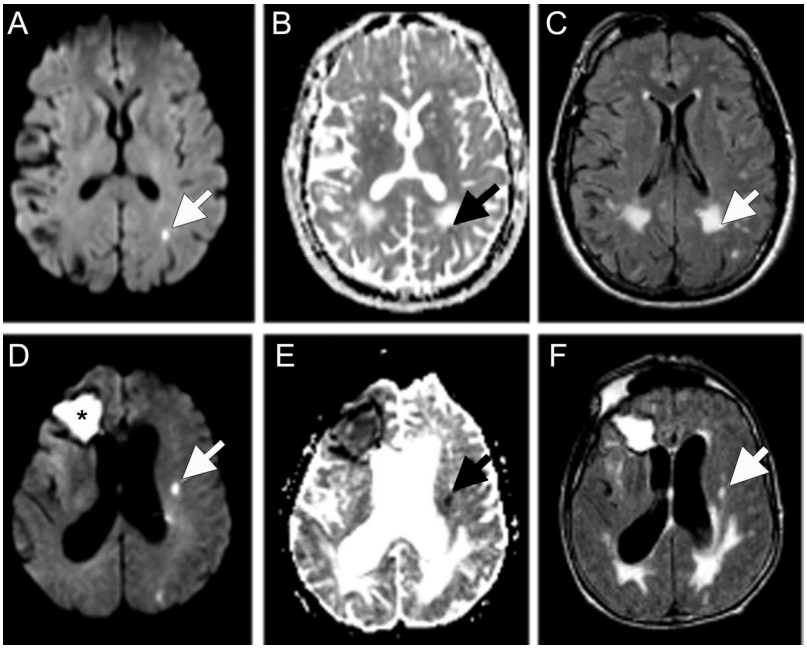
	CAA (n = 78)	AD/MCI (n = 55)	*p* Value
Age, y	78.2 ± 8.9	81.4 ± 8.1	0.04
Sex, male	32 (41)	24 (44)	>0.2
Hypertension	45 (58)	25 (45)	>0.2
Diabetes mellitus	5 (6)	4 (7)	>0.2
Dyslipidemia	25 (32)	19 (35)	>0.2
Tobacco use	23 (30)	13 (24)	>0.2
Coronary artery disease	12 (15)	8 (15)	>0.2
Prior ischemic stroke	6 (8)	2 (4)	>0.2
DWI (+)	12 (15)	0 (0)	0.001

Values are mean ± SD or n (%).
CAA = cerebral amyloid angiopathy; AD = Alzheimer disease; MCI = mild cognitive impairment; DWI (+) = presence of hyperintense lesion on diffusion-weighted imaging.

decreased (that is, hypointense) relative to the adjacent nonlesional brain parenchyma. Because of visible hemorrhages on scans of the CAA subjects, it was not possible for the reader to be blinded to diagnosis. We assessed interrater reliability for detection of DWI-positive lesions through independent review by a second experienced reader (N.S.R.) of a subset of 20 scans randomly selected from the CAA group. There was complete agreement between the readers on the presence (3 of the 20) and number (two lesions in 2 of the 3 positive cases) of DWI hyperintensities, indicating high interrater reliability (kappa = 1.0).

GRE images were also evaluated for total number of hemorrhagic lesions (microbleeds plus macrobleeds) and number of microbleeds (defined as hemorrhagic lesions ≤5 mm in diameter), as previously described.[23] Scans were converted to Analyze format using MRIcro (ww.mricro.com) for computer-assisted determination of FLAIR WMH volumes, using a combination of signal-intensity thresholding and manual editing, as described.[11] Absolute WMH volumes were normalized (nWMH) to correct for head size, using a previously validated method based on intracranial cross-sectional area.[24] The interrater reliability of this method was previously evaluated, with an intraclass correlation coefficient of 0.98.[11,25] FLAIR images were also analyzed for the presence of chronic infarcts, defined as hypointense lesions ≥3 mm with surrounding rim of FLAIR hyperintensity.[26]

Figure Representative MR images of silent ischemic infarcts in two patients with cerebral amyloid angiopathy



Each row of panels corresponds to axial diffusion-weighted imaging (DWI) (A and D), apparent diffusion coefficient (B and E), and fluid-attenuated inversion recovery (C and F) sequences from a single MRI scan. Panels A–C were obtained 3 months after a right frontal intracerebral hemorrhage in a 57-year-old man. Panels D–F were obtained 2 days after a right frontal intracerebral hemorrhage (asterisk in panel D) in a 70-year-old man. The arrows point to DWI-hyperintense lesions identified as subacute ischemic infarcts.

Statistical analysis. Nonparametric tests were chosen for analyses of number of hemorrhages and white matter volumes because of skewed distributions. Comparisons between cases and controls or between DWI-negative and DWI-positive cases were performed by *t* test (for age), Fisher exact test (for categorical variables), and Wilcoxon rank sum (for number of hemorrhages, nWMH volumes, and time interval between hemorrhage and scan). APOE genotype was analyzed as a categorical variable according to the presence or absence of the ε2 or ε4 alleles, with ε3/ε3 serving as a reference.[14]

RESULTS We analyzed 78 subjects with a diagnosis of probable CAA and 55 with AD or MCI for the presence of DWI-hyperintense lesions on MR imaging not performed for suspicion of ischemic infarction. AD/MCI subjects were approximately 3 years older on average than CAA subjects. The two groups otherwise had similar sex distribution, a nonsignificantly higher proportion of HTN in CAA than AD/MCI (58% vs 45%, $p > 0.2$), and otherwise similar proportions of vascular risk factors including diabetes, dyslipidemia, tobacco use, and coronary artery disease (table 1).

DWI-hyperintense lesions were present in 12 of the 78 CAA subjects (15%) vs 0 of the 55 with AD/MCI ($p = 0.001$). DWI lesions corresponded to hypointense foci on the ADC image and hyperintensities on FLAIR (figure), consistent with subacute infarction.[13] Five of the 12 DWI-positive CAA subjects demonstrated two lesions and 7 were solitary lesions, yielding a total of 17 DWI-hyperintense lesions. Of the 17 lesions, 11 were located in subcortical white matter, 4 in cortical gray matter, and 2 in cerebellum. None was closely related to a site of previous intracerebral hemorrhage.

We found no association within the CAA group between presence of a DWI-hyperintense lesion and age, sex, cognitive status before initial presentation, presence of HTN or severe HTN (defined as use of more than one antihypertensive medication), or any of the other vascular risk factors (table 2 and data not shown). The DWI-positive CAA subjects did, however, demonstrate more microbleeds (median 21 vs 3 microbleeds, $p = 0.019$) and more total (i.e., microbleed plus macrobleed) hemorrhagic lesions (median 22 vs 4 hemorrhages, $p = 0.025$) on GRE than

Table 2 Comparison of CAA subjects with and without DWI-hyperintense lesions

	All CAA (n = 78)	DWI (−) (n = 66)	DWI (+) (n = 12)	*p* Value*
Age, y, mean ± SD	78.2 ± 8.9	78.0 ± 8.5	79.6 ± 11.0	>0.2
Sex, male, n (%)	32 (41)	27 (41)	5 (42)	>0.2
Cognitive impairment before presentation, n (%)	24 (31)	8 (15)	4 (17)	>0.2
Total hemorrhages, median (25th, 75th percentiles)†	5 (2, 14)	4 (2, 12)	22 (4, 64)	0.025
Normalized WMH, cm^3, median (25th, 75th percentiles)	23.0 (11.4, 35.0)	23.0 (11.4, 34.7)	20.9 (7.8, 54.7)	>0.2
Presence of chronic infarcts, n (%)	14 (18)	12 (18)	2 (17)	>0.2
APOE ε2+ or ε4+, n (%; total available samples)	18 (46; n = 39)	15 (47; n = 32)	3 (43; n = 7)	>0.2

Cognitive status before presentation could not be determined in 1 of the 78 CAA subjects. DNA samples were available from 39 of the 78 CAA subjects.
*p Values compare DWI (−) vs DWI (+).
†Total hemorrhages represents sum of all hemorrhagic lesions (microbleeds plus macrobleeds) detected by gradient-echo MRI.
CAA = cerebral amyloid angiopathy; DWI (+) or DWI (−) = presence or absence of hyperintense lesion on diffusion-weighted imaging; WMH = white matter hyperintensity; APOE = apolipoprotein E genotype.

DWI-negative CAA subjects. No differences were seen between the DWI-positive and DWI-negative CAA groups on normalized volume of white matter T2 hyperintensities, presence of chronic infarcts on MRI, or distribution of APOE genotypes (table 2).

The presence of DWI-hyperintense lesions showed no association with recent (within 7 days) symptomatic ICH (32 of the 66 DWI-negative subjects scanned within 7 days of symptomatic ICH, vs 6 of the 12 DWI-positive subjects, $p > 0.2$) or with shorter time interval between symptomatic ICH and scan (median days [25th, 75th percentiles] 3 [1, 129] for DWI-negative subjects, 4.5 [2, 109] for DWI-positive subjects, $p > 0.2$). There was also no association of DWI lesions with MRI scans performed because of dizziness or confusion (5 of the 66 DWI-negative subjects were scanned for dizziness or confusion vs 2 of the 12 DWI-positive subjects, $p > 0.2$).

DISCUSSION The primary findings from this study were small DWI-hyperintense lesions suggestive of subacute ischemic infarction in 12 of 78 (15%) patients with a diagnosis of advanced CAA. Such lesions were absent from a slightly older AD/MCI control group. Their presence was unrelated to conventional vascular risk factors such as HTN, diabetes, or coronary artery disease and was instead associated with number of hemorrhagic lesions on GRE MRI, a marker of CAA severity.[23] As we excluded subjects with symptoms of ischemic stroke, these lesions appear to be clinically silent events that occur as part of the ongoing pathogenesis of CAA. These lesions appear similar to small silent infarcts identified in two patients with another small vessel disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.[27]

The signal characteristics, size, and location of the DWI-positive lesions suggest they may represent the neuroimaging correlates of the neuropathologic infarctions described in association with CAA.[2-7] Analyses of autopsied brains with advanced CAA have identified lesions described as perivascular scars, microinfarcts, or small infarctions at frequencies ranging from 37%[3] to close to 100%.[2,7] These pathologically observed infarctions are frequently multiple and located in the cortical ribbon or underlying subcortical white matter. The observation that CAA in cortical vessels can cause infarction of subcortical white matter presumably reflects the anatomy of blood flow to the white matter, by which penetrating vessels traverse the cortex before supplying the white matter.[28] Although one neuropathologic analysis found a possible synergistic relationship between severe CAA and HTN,[3] these lesions appear generally to occur independently of atherosclerosis or arteriolosclerosis of cerebral or systemic vessels. Blood pressure did not appear to be a major contributor to DWI-positive lesions in the current study, though this study did not include direct blood pressure measurements at the time of MRI.

Given the transience of DWI changes after stroke, the finding of lesions in 15% of subjects suggests these small infarctions may occur very frequently. Assuming a 10-day poststroke period when restricted diffusion remains detectable,[13] their estimated annual prevalence would be calculated as (17/78) x (365/10) or 8.0 new infarctions per person-year. This estimate is strikingly high relative to the estimated incidence of new microbleeds (~1.4 per year) or symptomatic ICH (~0.14 per year) calculated from other cohorts with advanced CAA[23] and suggests that the lifetime burden of ischemic infarction in advanced CAA could be substantial.

This surprisingly high frequency of DWI lesions raises important questions about our study's limitations and possible sources of overestimation. The number of scans examined was relatively small, yielding wide confidence intervals for the true prevalence of DWI-positive lesions (exact 95% confidence intervals 8.2% to 25.3%). Also, there was no pathologic confirmation that the DWI-positive lesions indeed represent infarctions, although their signal characteristics and location correlate reasonably well with the neuropathologic studies of CAA. We further note possible bias toward identifying lesions in the CAA cases, particularly as the scans could not be

analyzed blinded to the accompanying presence of hemorrhage. It is reassuring in this regard that independent analysis of a subset of scans showed no evidence for substantial interrater variability. Finally, scans were generally obtained at only a single time point in each subject. Only 10 of the 78 MRI scans were performed without any reference to clinical events, and the majority were performed during the days (38 scans) or months (18 scans) after acute ICH. We did not, however, see an increased frequency of DWI lesions on scans performed shortly after ICH relative to the remainder of the study group, indicating that the timing of infarction and ICH may be independent of each other.

The association between DWI-positive lesions and number of total hemorrhages or microbleeds suggests that infarction and microbleed formation may share common pathophysiologic steps. Previous pathologic studies have identified vasculopathic changes specifically linked to CAA-related bleeding such as fibrinoid necrosis and microaneurysm formation[29]; the association of these pathologic changes with small infarction remains to be determined. The absence of association between DWI lesions and WMH is somewhat unexpected, as one might have predicted a close relationship between the occurrence of true infarction and the incomplete infarction hypothesized to underlie WMH.[28] Our data instead suggest that processes besides microinfarction may be key determinants of WMH burden, one example being impaired cerebrovascular reactivity[12] (which is associated with volume of WMH). We also found no association between MRI evidence of chronic infarcts and the DWI-positive lesions, which may be too small to leave an area of MRI signal recognizable as a chronic infarct.

The suggestion of relatively frequent ischemic infarction in CAA subjects extends the spectrum of CAA-related pathophysiology, which previously included hemorrhage and impaired cerebrovascular reactivity. Our cross-sectional data provide no information on the effect of these lesions on future clinical course, clearly an important subject for future investigation. Determining the contribution of small ischemic infarction to cognitive impairment in CAA will likely require multivariable analysis in larger cohorts, controlling for other radiographic markers of microstructural damage in CAA such as white matter lesions[30] and increased global mean diffusivity.[22] If these lesions are found to contribute substantially to the clinical impact of CAA, they may ultimately be considered as radiographic markers for candidate treatments of this disorder.

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